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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/730,549	12/05/2003	Mary J. Laughlin	CWRU-P01-046	1488

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EXAMINER	
BARNHART, LORA ELIZABETH	
ART UNIT	**PAPER NUMBER**
1651	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/730,549	LAUGHLIN ET AL.	
	Examiner	Art Unit	
	LORA E. BARNHART	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,8-12,17-43,46-57 and 62-69* is/are pending in the application.

4a) Of the above claim(s) *5,9,18,22,37-39 and 48* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,8,10-12,17,19-21,23-36,40-43,46,47,49-57 and 62-69* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 November 2007* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/7/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The notice of noncompliant amendment mailed 1/14/08 was sent in error. This notice is hereby withdrawn.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 11/5/07 has been entered.

Response to Amendments

Applicant's amendments filed 11/5/07 to claims 1-3, 5, 8-12, 24-26, 28, 29, 31-33, 37, 38, 47, 62, and 65-68 have been entered. Claims 13, 14, 16, and 45 have been cancelled in this reply. No claims have been added. Claims 1-5, 8-12, 17-43, 46-57, and 62-69 remain pending in the current application, of which claims 1-4, 8, 10-12, 17, 19-21, 23-36, 40-43, 46, 47, 49-57, and 62-69 are being considered on their merits. Claims 5, 9, 18, 22, 37-39, and 48 remain withdrawn from consideration at this time. Prior art references not included with this Office action can be found in a prior action.

Specification

The objections to the specification are withdrawn.

Claim Rejections - 35 USC § 112

The rejections of record under 35 U.S.C. § 112 are withdrawn in light of the claim amendments.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 12 and 46 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 12 requires that the $CD34^+CD133^+$ cells be "$CD31^+$, $CD146^+$, $CD133^+$, $CD34^+$, VE-$cadherin^+$, or a combination thereof." This claim includes embodiments in which, e.g., the $CD34^+CD133^+$ cells are $CD34^+$ but not $CD133^+$, which is confusing. Similarly, claim 46 does not appear to further limit claim 1.Clarification is required.

Drawings

The drawings were received on 11/5/07. These drawings are acceptable.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-4, 8, 10-12, 17, 19-21, 23-36, 40-43, 46, 47, 49-57, and 62-69 are/remain rejected under 35 U.S.C. 103(a) as being unpatentable over Strauer et al. (2002, *Circulation* 106: 1913-1918; reference CAAA on 12/3/04 IDS) taken in view of Ueno et al. (U.S. Patent Application Publication 2002/0037278), Kocher et al. (2001, *Nature Medicine* 7: 430-436), and Itescu (2003, U.S. Patent Application Publication 2003/0199464; reference AM on 12/3/04 IDS).

Strauer et al. teach isolating bone marrow (BM) from humans (page 1914, column 1, paragraph 5); isolating bone marrow mononuclear cells (BMCs) therefrom; cultivating them overnight in a buffered tissue culture medium comprising autologous serum (page 1914, column 2, paragraph 1), and administering over 10^6 BM-MNCs to the ischemic tissue using a balloon catheter, specifically via intracoronary administration at ischemic myocardium in a subject in need thereof (page 1914, column 2, paragraph 2; page 1915, column 2, paragraph 3). Strauer et al. teach administering between $1.5x10^6$ and $4x10^6$ BM-MNCs 6 or 7 times, *i.e.*, between $9x10^6$ and $2.8x10^7$ BM-MNCs; Strauer et al. also teach that 0.65% of BM-MNCs are $AC133^+$ ($CD133^+$). Therefore, Strauer et al. teach administering between $5.9x10^4$ and $1.8x10^5$ $AC133^+$ EPCs. Strauer et al. teach that said injections resulted in improved cardiac function, cardiac geometry, and contractility (page 1915, column 2). Strauer et al. teach that their BMCs comprise

mesenchymal stem cells (MSCs) as well as endothelial progenitor cells (EPCs; page 1916, column 2, paragraph 2).

Strauer et al. do not teach enriching $CD34^+CD133^+$ EPCs at least two-fold prior to administration to the subject. Strauer et al. do not teach administering cells in the ratios recited in claims 28, 53, 67, and 68. Strauer et al. do not teach all of the modes of administration recited in claims 29-32. Strauer et al. do not teach coadministering the cells with VEGF or any recombinant polypeptide, as in claims 40-43. Strauer et al. do not teach administering allogeneic EPCs.

Ueno et al. teach methods for treating ischemic tissues by administering bone marrow mononuclear cells; Ueno et al. teach that the administration may be local or systemic and may be carried out via injection or infusion into arteries or veins, directly into an occlusion, or application into a tissue or organ of interest (paragraphs 0034 and 0035). Ueno et al. teach that large amounts of cells may be administered to patients safely (paragraph 0037) and that the number of cells administered is optimizable (paragraph 0034). Ueno et al. teach coadministering recombinant VEGF with the BMCs (paragraph 0042).

Kocher et al. teach that bone-marrow-derived angioblasts, which express AC133 (i.e., CD133) and CD34, among other markers (page 431, column 2, last sentence), promote revascularization of infarcted myocardium (Abstract; page 432, column 2, paragraph 2; Figure 3). Kocher et al. teach that angioblasts isolated to 98% purity express AC133 (page 435, column 1, paragraph 4). Kocher et al. teach that

administration of their $CD34^+$ $AC133^+$ cells may be combined with other therapies (Abstract; page 435, column 1, paragraph 3).

Itescu teaches methods for regenerating myocardial tissue after ischemic damage by promoting neovascularization with an injection of endothelial progenitor cells (paragraph 0055). The EPCs of Itescu are found in bone marrow (paragraph 0056), express CD34 and CD133 (paragraph 0061), and may be allogeneic with respect to the recipient (paragraph 0057). Itescu teaches that the number of cells administered to the patient may vary (paragraph 0056), as may the location of the injection (paragraph 0061).

A person of ordinary skill in the art would have had a reasonable expectation of success in enriching the $CD34^+CD133^+$ EPCs within the BM-MNCs of Strauer et al. at least twofold because Kocher et al. teach methods for enriching such cells to 98% purity. The skilled artisan would have been motivated to enrich the $CD34^+CD133^+$ EPCs in the administered composition of Strauer et al. because Kocher et al. recognized that $CD133^+$ cells promote neovascularization of ischemic tissue; therefore, administering more cells known at the time of the invention to achieve the desired result of Strauer et al. would improve the outcome of the method of Strauer et al.

The person of ordinary skill in the art would have had a further reasonable expectation of success in coadministering the VEGF of Ueno et al. with the cells of Strauer et al. in the method of Strauer et al. because Ueno et al. teach methods for administering recombinant polypeptides and that such polypeptides may be coadministered with cells. The skilled artisan would have been motivated to include

VEGF with the stem cells in the method of Strauer et al. because Ueno et al. teach that VEGF is a growth factor that promotes neovascularization upon administration to a patient.

The person of ordinary skill in the art would have had a further reasonable expectation of success in administering allogeneic cells in the method of Strauer et al. because Itescu teaches that allogeneic EPCs promote neovascularization. The skilled artisan would have been motivated to administer allogeneic EPCs in the method of Strauer et al. for the expected benefit that the pool of donor cells would be dramatically increased in size.

The selection of the mode of administration of the cells in the method of Strauer et al. would have been a routine matter of optimization on the part of the artisan of ordinary skill, said artisan recognizing that Ueno et al. and Itescu both teach that ischemia may be treated bone marrow-derived cells administered in any of a variety of means. A holding of obviousness over the cited claims is therefore clearly required.

The selection of the number of each type of cell to administer in the method of Strauer et al. would have been a routine matter of optimization on the part of the artisan of ordinary skill, said artisan recognizing that Strauer et al., Ueno et al., and Itescu all teach that these numbers may be modified depending on the desired outcome. A holding of obviousness over the cited claims is therefore clearly required.

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was made to enrich the $CD34^{+}CD133^{+}$ EPCs from the BM-MNCs of Strauer et al. using the methods of Kocher et al. and administer more such

$CD34^+CD133^+$ EPCs with the mesenchymal stem cells in the method of Strauer et al. because Kocher et al. teach that $CD34^+CD133^+$ EPCs promote neovascularization. It would have been further obvious to coadminister recombinant VEGF with the cells in the method of Strauer et al. because Ueno et al. teach that VEGF is a growth factor that promotes neovascularization and aids in treating ischemia. It would have been further obvious to administer allogeneic EPCs in the method of Strauer et al. because Itescu teaches that allogeneic EPCs promote neovascularization. Finally, it would have been further obvious to vary the numbers of each type of cell administered and the mode of administration because Strauer et al., Ueno et al., and Itescu concur that these are optimizable variables for the reasons discussed above.

Therefore, the invention as a whole would have been *prima facie* obvious to a person of ordinary skill at the time the invention was made.

Applicant alleges that Strauer et al. did not specifically recognize that the $CD34^+CD133^+$ EPCs within their BM-MNCs contributed to the neovascularization they observed (Reply, page 15, paragraph 3). Applicants allege that Kocher et al. and Itescu et al. do not teach purifying $CD34^+CD133^+$ cells (Reply, page 15, paragraph 4 et seq.). These arguments have been fully considered, but they are not persuasive.

Applicant's comments regarding the level of purity of the $CD34^+CD133^+$ EPCs administered by the prior art methods are addressing limitations not recited in the claims. The claims are drawn to a method that comprises administering "enriched $CD34^+CD133^+$ EPCs and enriched MSCs." None of the claims require that the $CD34^+CD133^+$ EPCs be purified. Furthermore, the claims are drawn to a method

"comprising" administering $CD34^+CD133^+$ EPCs; the transitional term "comprising" is inclusive or open-ended and does not exclude additional, unrecited elements or method steps. See, *e.g.*, *Invitrogen Corp. v. Biocrest Mfg.*, L.P., 327 F.3d 1364, 1368, 66 USPQ2d 1631, 1634 (Fed. Cir. 2003) and M.P.E.P. §2111.03.

In response to applicant's argument that Strauer et al. did not recognize the benefit of administering $CD34^+CD133^+$ EPCs to infarcted tissue, the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985). In other words, the fact that applicant identified a putative active ingredient within the composition administered in the method of Strauer does not make the method per se patentable, especially in light of the teachings of the secondary references, which indicate that $CD34^+CD133^+$ EPCs were known in the art at the time of the invention to promote neovascularization and to treat ischemia.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-4, 8, 10-12, 17, 19-21, 23-28, 35, 40-43, 46, 47, 49-57, and 62-69 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 3, 8, 9, 11-16, and 18-26 of copending Application No. 10/875,643, which shares inventors and current assignment with the instant application. Although the conflicting claims are not identical, they are not patentably distinct from each other because the scope of the claims of the instant application overlaps that of the claims in the '643 application.

Independent claims 1 and 8 in the '643 application are drawn to a method for improving blood flow to ischemic myocardium by administering $CD34^+CD133^+$ cells enriched at least twofold from bone marrow via infusion to a coronary artery; instant independent claim 54 is drawn to a method nearly identical to the '643 method, but in instant claim 54, the properties of the artery are more particularly pointed out. Instant independent claims 1 and 57 are drawn to methods of treating ischemic tissue and inducing blood vessel formation in ischemic tissue, respectively, by administering $CD34^+CD133^+$ cells along with mesenchymal stem cells (MSCs). Claims 12-14 of the '643 application depend from claim 8 and require coadministration of MSCs with the $CD34^+CD133^+$ cells.

Instant claims 19, 20, 47, and 49 require culture expansion of the cells prior to administration, as do claims 22-24 of the '643 application. Instant claims 24-28, 53, 64, 67, and 68 limit the number of cells administered, as do claims 25 and 26 of the '643 application. Instant claims 40-43 require coadministration of a recombinant polypeptide that may be VEGF; claims 15 and 16 of the '643 application require coadministration of a growth factor that may be VEGF. Instant claim 4 and claim 3 of the '643 application appear to merely recite inherent effects of the claimed methods.

It is noted that the claims in the '643 application are drawn to methods that comprise administering cells isolated from umbilical cord blood, bone marrow, or peripheral blood, while the cells administered in the instant methods are claimed as being isolated from bone marrow. The source of the cells is a product-by-process limitation that does not distinguish the cells administered in the instant method with those administered in the '643 method absent a substantive evidentiary showing that $CD34^{+}CD133^{+}$ cells isolated from bone marrow are patentably distinct from those isolated from other sources. See M.P.E.P. § 2113. Instant claims 1, 3, 17, 54, 56, and 57 and claims 1, 8, and 12 of the '643 application include product-by-process limitations.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

No claims are allowed. No claims are free of the art.

Applicant is requested to specifically point out the support for any amendments made to the disclosure in response to this Office action, including the claims (MPEP

714.02 and 2163.06). In doing so, applicant is requested to refer to pages and line numbers in the as-filed specification, **not** the published application. Due to the procedure outlined in MPEP § 2163.06 for interpreting claims, it is noted that other art may be applicable under 35 U.S.C. § 102 or 35 U.S.C. § 103(a) once the aforementioned issue(s) is/are addressed.

Applicant is requested to provide a list of all copending U.S. applications that set forth similar subject matter to the present claims. A copy of such copending claims is requested in response to this Office action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lora E. Barnhart whose telephone number is 571-272-1928. The examiner can normally be reached on Monday-Thursday, 9:00am - 5:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lora E Barnhart/
Primary Examiner, Art Unit 1651